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EXAMINER	
CANELLA, KAREN A	
ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 10/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/988,008	DINKELBORG ET AL.	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *4* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 5-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/9/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Acknowledgement is made of applicant's election with traverse of Group I, claims 1-3 and 5-24, drawn to compounds and use of compounds of the formula comprising 'Cys-Ser-Ser-Leu-Met-Asp-Lys-Glu-Cys' motif within a cyclic peptide. The traversal is on the grounds that the restriction is improper because if would not be undue burden to search all of the individual compounds and methods of using said compounds. This has been considered and found partially persuasive. The restriction requirement of the Paper of June 25, 2004 is withdrawn and hereby replaced with the following election of species.

This application contains claims directed to the following patentably distinct species of the claimed invention:

I. Claims 1-3, 5-24, drawn to compounds and use of compounds of the formula comprising a 'Cys-Ser-Ser-Leu-Met-Asp-Lys-Glu-Cys' motif within a cyclic peptide,

II. Claims 1-3, 5-24, drawn to compounds and use of compounds of the formula comprising a 'Cys-Ser-Ser-Trp-Leu-Asp-Lys-Glu-Cys' motif within a cyclic peptide,

III. Claims1-3, 5-24, drawn to compounds and use of compounds of the formula comprising a 'Cys-Phe-Thr-Tyr-Lys-Asp-Lys-Glu-Cys' motif within a cyclic peptide,

IV. Claims 1-3, 5-24, drawn to compounds and use of compounds of the formula comprising a 'Cys-Asn-Ser-Trp-Leu-Asp-Lys-Glu-Cys' motif within a cyclic peptide,

V. Claims 1-3, 5-24, drawn to compounds and use of compounds of the formula comprising a 'Cys-Lys-Asp-Met-Thr-Asp-Lys-Glu-Cys' motif within a cyclic peptide,

VI. Claims 1-3, 5-24, drawn to compounds and use of compounds of the formula comprising a 'Cys-Val-Tyr-Phe-Cys' motif within a cyclic peptide,

VII. Claims 1-3, 5-24, drawn to compounds and use of compounds of the formula comprising a 'Cys-Asn-Asp-Met-Tyr-Ala-Glu-Glu-Cys' motif within a cyclic peptide,

VIII. Claims 1-3, 5-24, drawn to compounds and use of compounds comprising cyclo (Trp-Asp-Pro-Val-Leu), cyclo (Glu-Ala-Ile-Leu-Trp) and cyclo (Trp-Asp-Pro-2-thienyl-Gly-Leu),

IX. Claims 1-24, drawn to compounds and use of compounds comprising a linear peptide wherein said linear peptide binds endothelin receptors,

X. Claims 1-3, 5-24, drawn to compounds and use of compounds comprising pyrimidinyl-benzenesulfonamide radical, bipyrinidin-4-yl-benezenesulfonadmide radical, caffeoylmyricerone radical or a (2-pyridyl)-propionic acid radical,

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, all claims are generic.

Applicant is advised that a reply to this requirement must include an identification of the species that is elected consonant with this requirement, and a listing of all claims readable thereon, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

2. Applicants election of Group I in the Paper Filed July 20, 2004, is taken as an election of species No.1. It is noted that species No. 1 includes compounds 1, 7, 25 and 26 of the compounds listed in claim 3 and compounds 1, 9, 25 and 26 of the compounds listed in claim 10. After a review of the elected species in light of the prior art, the examined species will include compounds 1-3, 6-14, 16, 17, 25 and 26 of claims 3 and 10. Claims 1-25 are pending. Claim 4, drawn to non-elected species, is withdrawn from consideration. Claims 1-3 and 5-24 are under consideration.

Claim Rejections - 35 USC § 101

3. 35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

4. Claims 1-3, 5-8 are rejected under 35 U.S.C. 101 because they are not presented in the format of a proper process claim. See MPEP 2173.05(q).

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-3 and 5-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(A) Claims 1-3, 5-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 1-3, 5-8 drawn to the "use of the compounds" are vague and indefinite. The claims are drawn to a method of using an agent, but fail to set forth any active, positive steps that define the claimed method.

(B) Claims 1 and 9 recite "endothelin analogs" and "endothelin derivatives". The metes and bounds of both "endothelin analogs" and "endothelin derivatives" are unclear. The specification does not provide a limiting definition of the structural requirements of either the endothelin analog or the endothelin derivative. Further, it is unclear if endothelin derivative encompasses solely endothelin with the addition of auxiliary molecular groups or if "derivative" encompasses structural alterations within the known structure of endothelin. It is unclear if endothelin analogs must possess all the functional characteristics of endothelin or if endothelin analogs may possess only a limited number of functional characteristics of endothelin.

(C) Claim 1 recites the formula E-Wn. Claim 9 recites the formula E-W1n. It is unclear if E-W signifies a covalent bond, or if E-W encompasses complexes between E-W on a non-covalent nature. For purpose of examination, all alternatives will be considered.

(D) Claims 1 and 9 recite "or that is derived from a chemotherapy agent". It is unclear if "derived from a chemotherapy agent" means that the chemotherapy agent is encompassed in its entirety, or if "derived from" includes structural alterations of said chemotherapy agent.

(E) It is unclear if all the species recited within the paragraph beginning with "W stands for" in claims 1 and 9 are set forth in the alternative, because the conjunction "or" is used in the first line of said paragraph in claim 1 and the second line of said paragraph in claim 9 and the last line of each of the paragraphs. If applicant intends that the species are named in the alternative, applicant is advised only to use the "or" between the penultimate and the ultimate species. For purpose of examination, the claim will be read as naming the species in the alternative.

(F) Claim 1 is vague and indefinite in the recitation of "n stands for numbers 1-100, preferably 1-10 as therapeutic agents". It is unclear how "preferably 1-10 as therapeutic agents" defines the metes and bounds of the index number 10 which is stated to be numbers from 1-100.

(G) Claim 9 is vague and indefinite in the recitation of "n stands for numbers 1-100, preferably 1-10". It is unclear how the term preferably 1-10 limits the metes and bounds of the number n which is set forth as a number from 1-100.

(H) Claim 5 is vague and indefinite because it can't be discerned if the "and/or gamma radiator" applies to the beta only, or if it applies collectively to the beta and alpha. Further it is unclear if and "and/or" is limited only the gamma radiator species, or if it applies to the positron radiator, the Auger radiator, etc. Further, it is unclear if the "and/or fluorescence radiator" applies to only the x-ray radiator, or if it applies collectively to the gamma radiator, positron radiator, auger electron radiator and x-ray radiator collectively.

(I) Claims 13-23 recite "in which the active group is derived from...". It is unclear if "derived from" represents the entirety of the recited compounds in addition to auxiliary molecular groups, or if "derived from" encompasses structural alteration of said recited compounds.

(J) Claim 14 is vague and indefinite because the compounds "hexamethylmelanine" and "sumarin" are not recognized in the art.(K) Claim 24 is vague and indefinite in the recitation of

"commonly used" in galencials. The metes and bounds of "commonly used" have not been set forth by the specification.

(K) Claim 24 is vague and indefinite in the recitation of "commonly used" in galencials. The metes and bounds of "commonly used" have not been set forth by the specification. (K) Claim 24 is vague and indefinite in the recitation of "commonly used" in galencials. The metes and bounds of "commonly used" have not been set forth by the specification.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-3 and 5-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for how to make polypeptides which bind to the endothelin receptor and are fused or conjugated to an active agent which is a polypeptide, does not reasonably provide enablement for non-peptide molecules which bind to endothelin receptors which are fused or conjugated to active agents and polynucleotides which bind to endothelin receptors which are fused or conjugated to active agents which are not radionuclides or polypeptides. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 9-24 are drawn to compounds of the formula E-W1n. Claims 1-3 and 5-8 are drawn to methods of using compounds of the formula E-W. When given the broadest reasonable interpretation, claims 1-3 and 5-8 are drawn to methods of using compounds having a covalent linkage between E and W and claims 9-24 encompass compounds having a covalent linkage between E and W1. While it is recognized in the art that the placement of an active agent such as a radionuclide directly on a protein such as antibody would not necessarily alter the ability of the antibody to bind to its target protein, it is also recognized in the art that direct chemical conjugation of active agents such as drugs will alter or negate the desired activity of said drugs. Further, it is also recognized in the art that the chemical modification of ligands which bind to a receptor can also result in the loss of receptor-binding ability. It is noted that claims are not

limited to endothelin agonists, antagonists, or analogues which are proteins and peptides and thus encompass molecules beyond of the scope of proteins and peptides. For instance, The specification has not enabled the scope of the claims which encompasses a covalent linkage between "E" and "W" or "W1". Accordingly, the specification has not enabled the scope of the method claims dependent upon aforesaid product.

The M.P.E.P. (2164.08(b)) states

Although, typically, inoperative embodiments are excluded by language in a claim (e.g., preamble), the scope of the claim may still not be enabled where undue experimentation is involved in determining those embodiments that are operable. A disclosure of a large number of operable embodiments and the identification of a single inoperative embodiment did not render a claim broader than the enabled scope because undue experimentation was not involved in determining those embodiments that were operable. In re Instant, 537 F.2d 498, 502-503, 190 USPQ 214, 218 (CCPA 1976). However, claims reading on significant numbers of inoperative embodiments would render claims non-enabled when the specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative. Atlas Powder Co. v. E.I. duPont de Nemours & Co., 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984); In re Cook, 439 F.2d 730, 735, 169 USPQ 298, 302 (CCPA 1971).

In the instant case, the method claims are lacking a method objective stated in the preamble. The specification does not clearly identify the operative versus inoperative embodiments. Further, for the reasons set forth above, regarding the lack of teachings of how to make the required compounds of the formula E-W wherein E is attached by a covalent linkage to W, without negation of the receptor binding ability of E and therapeutic activity of W, the claims are directed to both the operative and non-operative embodiments. Thus, one of skill in the art would be subject to undue experimentation in order to make and use the claimed compounds and methods.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

9. Claims 1-3, 5-12, 19, 23 and 24 rejected under 35 U.S.C. 102(b) as being anticipated by Erber et al (WO 94/22491, reference of trhe IDS filed April 9, 2002).

Claim 1 is drawn to use of the compounds of the general formula I in which E stands for a radical that binds endothelin receptors and is derived from endothelins, endothelin analogs, derivatives, partial sequences and antagonists, and wherein W stands of an active group that is a radionuclide, derived from a chemotherapy agent, a complex with a radioactive metal isotope, an antibody, an antibody fragment, a peptide, a carbohydrate, an oligonucleotide, a PTK blocker, an antithrombotic agent, a clotting cascade inhibitor, a hormone, a growth factor inhibitor, a pharmaceutical agent, an anti-inflammatory agent, a Ca-antagonist, a lipid-lowering agent or an anti-proliferative agent, wherein the index number n, is 1-100.

Claim 2 is drawn to use of the compounds of the formula E-Wn in which E, W and n have the same meaning as in claim 1 for the treatment of vascular diseases. Claim 5 is drawn to use according to claim 1 in which the active group contains an alpha, beta, gamma, position, Auger electron, x-ray or fluorescent radiator. Claim 3 is drawn to use of the compounds of claim 1 in which the radical that binds the endothelin receptor has the recited structures. Claim 5 is drawn to use according to claim 1 in which the active group contains an alpha-beta. Claims 6 and 7 drawn to use according to claim 5 in which the active group contains a recited element. Claim 8 is drawn to use of claim 5 wherein the radionuclide is 188-Re, 90-Y, or 111-In.

Claim 9 is drawn to compounds of the general formula E-W1n in which E stands for a radical that binds endothelin receptors and is derived from endothelins, endothelin analogs, derivatives, partial sequences and antagonists, and wherein W1 stands of an active group that contains a radionuclide of the elements At, Ba, Br, C, F, N, O or P, derived from a chemotherapy agent, an antibody, an antibody fragment, a peptide, a carbohydrate, an oligonucleotide, a PTK blocker, an antithrombotic agent, a pharmaceutical agent, a hormone, a growth factor inhibitor, a platelet aggregation inhibitor, an anti-inflammatory agent, a Ca-antagonist, a lipid-lowering agent or an anti-proliferative agent, wherein the index number, n, is 1-100. Claim 10 embodies the compounds of claim 9 having the recited structures. Claim 11 embodies the compounds of claim 9 wherein the active group contains a radionuclide of the elements At, Ba, Br, C, F, N, O or P. Claim 12 embodies the compound of claim 9 wherein the active group s vinblastine, doxorubicin, bleomycin, methorexate, 5-fluorauracil, 6-thioguanine, cytarabine, cyclophosphamide or a cis-platinum radical. Claim 19 embodies the compound of claim 9 wherein the active group is derived from a corticoid or a non-steroidal anti-inflammatory. Claim

23 embodies the compound of claim 9 wherein the active group is derived from an aptamer or antisense nucleotide.. Claim 24 embodies the compound of claim 9 which is dissolved, emulsified or suspended in an aqueous medium and the adjuvants, additives and/or stabilizers that are commonly used in galenicals.

Erber et al disclose the compounds of 1-3, 6-14, 16, 17 and 25 of claims 3 and 10 (pages 14-15) administered with bleomycin, antibodies, steroid hormones, DNA, and RNA (page 22, lines 15-31) which fulfills the specific embodiment of claim 23. Erber et al disclose the use of said compounds for tumor therapy (page 22, lines 33-35). Erber et al disclose the conjugation of the compounds with technicium 99m (page 23, lines 27-35) and 188-Rhenium (page 25, lines 5-13) which fulfills limitations of claims 1, 5-8 and 9. It is noted that the metes and bounds of claims 1 and 9 are unclear with reference to the nature of the bond between E and W or E and W1. Thus, the administration of the peptides as disclosed by Erber in combination with bleomycin, antibodies, steroid hormones, DNA, and RNA fulfills the specific embodiment of the active group in that the active group is administered with the peptide and thus would associate with said peptides by ionic and hydrogen bonding.

10. Claims 1, 2, 9, 19 and 24 are rejected under 35 U.S.C. 102(b) as being anticipated by Porter et al (WO 96/22978).

The specific embodiments of claims 1, 2, 9, 19 and 24 are set forth above.

Porter et al disclose compounds of Formula I as antagonists of endothelin (abstract). Porter et al disclose that because endothelin is produced by tumor cells, and in light of its mitogenic properties, endothelin receptor antagonists would be useful adjuncts in cancer chemotherapy (page 4, lines 6-9). Porter et al disclose that the compounds if the invention are useful in the treatment of a patient suffering from conditions which can be ameliorated by the administration of an endothelin inhibitor (page 18, line 7 to page 19, line 9). Porter et al disclose that the a preferred embodiment of Formula I has a CN group for R1. Porter et al disclose suspensions and emulsions of the disclosed endothelin inhibitors for parenteral administration (page 20, line 32 to page 21, line 12) that fulfill the specific embodiment of claim 24. Porter et al disclose hat the compounds of the invention can be administered in combination with angiotensin II receptor antagonist, renin inhibitors, angiotensin converting enzyme inhibitors,

alpha and beta-adrenoceptor agonists and antagonists, diuretic, potassium channel activator, calcium channel antagonists, nitrates, antiarrhythmic agents, positive inotropic agents, serotonin receptor agonists and antagonists, platelet activating factor antagonists, antithrombotic and antithrombolytic agents, lipid lowering agents and immunosuppressive agents (page 22, line 31 to page 23, line 15). It is noted that the metes and bounds of claims 1 and 9 are unclear with reference to the nature of the bond between E and W or E and W1. Thus, the administration of the antagonists of endothelin as disclosed by Porter et al in combination with the angiotensin II receptor antagonist, renin inhibitors, angiotensin converting enzyme inhibitors, alpha and beta-adrenoceptor agonists and antagonists, diuretic, potassium channel activator, calcium channel antagonists, nitrates, antiarrhythmic agents, positive inotropic agents, serotonin receptor agonists and antagonists, platelet activating factor antagonists, antithrombotic and antithrombolytic agents, lipid lowering agents and immunosuppressive agents fulfills the embodiment of E-W wherein the bonding between E and W is ionic and hydrogen bonding rather than a covalent bond.

11. Claims 1-3, 9, 10, 16, 20 and 24 rejected under 35 U.S.C. 102(e) as being anticipated by Chwalisz et al (US 5,811, 416).

The specific embodiments of claims 1-3, 9, 10 and 24 are set forth above. Claim 16 embodies the compound of claim 9 wherein the active group is derived from a RGD peptide or from an acetylsalicylic acid. Claim 20 embodies the compound of claim 9 wherein the active group is estradiol. Chalisz et al disclose methods of treatment comprising administering pharmaceutical composition comprising an endothelin antagonist in combination with a progestin and aspirin which fulfill the specific embodiments of claims 1 and 9 with regard to hormones and claim 16 with regard to "derived from acetylsalicylic acid" (column 8, line 62 to column 9, line 20). Chwalisz et al specifically disclose estradiol as part of the disclosed combination (column 9, lines 41-44 and column 10, lines 7-19), thus fulfilling the specific embodiments of claim 20. Chwalisz et al disclose cyclo (D-Trp-D-Asp-Pro-D-Val-Leu) as a selective ETA antagonist (column 4, lines 51-57), which fulfills the specific embodiment of claims 1 and 9. Chwalisz et al disclose suspensions and emulsions for parental administration (column 11, lines 34-37). The disclosure of Chwalisz et al fulfills the specific embodiment of

the formulas E-W and E- W1 because it is unclear if claims 1 and 9 require a covalently linkage between the radical and the active group.

12. Claims 1, 3, 9, 10, 12, 14 and 24 are rejected under 35 U.S.C. 102(b) as being anticipated by Harvey et al (WO 96/09818).

The specific embodiments of claims 1-3, 9, 10, 12 and 24 are set forth above. Claim 14 embodies the method of claim 9 wherein the active group is derived from the listed compounds which include folic acid antagonists.

Harvey et al disclose that substances which specifically inhibit the binding of endothelin to its receptor are believed to block the physiological effects of endothelin and are useful in treating patients with endothelin related disorders (page 3, lines 14-17, page 73, lines 19-23). Harvey et al disclose a multitude of peptidic and non-peptide endothelin antagonists (page 3, line 18 to page 18). Harvey et al disclose a method of treating emesis comprising administering a pharmaceutical composition comprising an endothelin antagonist in combination with a tachykinin antagonist, a substance P antagonist, a neurokinin antagonist or a 5HT3 antagonist (page 95, lines 9-16). Harvey et al specific disclose BQ-123 as a endothelin antagonist, thus fulfilling the specific embodiment of claims 3 and 10, drawn to cyclo [D-Tryp-D-Asp-Pro-D-Val-Leu]. Harvey et al disclose that a preferred embodiment of an endothelin antagonist of the combination are the compounds of formula I useful in the treatment of emesis induced by anti-neoplastic agents such as cis-platin and folic-acid antagonists (page 97, lines 7-31). Harvey et al disclose that the combination therapy may be administered together with the chemotherapeutic agent for simultaneous use for the relief of emesis induced by the chemotherapeutic agent (page 98, lines 3-11), thus fulfilling the specific embodiments of claims 1 and 9 because claims 1 and 9 encompass the endothelin antagonists in association with the active agent, and a mixture of the antagonist with the active agent fulfills the specific embodiments of the claims.

13. Claims 1, 2, 9, 20 and 24 are rejected under 35 U.S.C. 102(e) as being anticipated by Bradbury (EP 682,016 A1).

The specific embodiments of claims 1, 2, 9 and 24 are set froth above. Claim 20 embodies the method of claim 9 wherein the active group is derived from cochicine, angiopeptin, estrodiol or an ACE inhibitor.

Bradbury discloses a method of treating diseases in which abnormal levels of endothelin play a causative role comprising the administration of endothelin antagonists of formula I, wherein examples of said diseases are hypertension, pulmonary hypertension, congestive heart failure, dyslipidaemia, artherosclerosis, restinosis, acute and chronic renal failure, stroke, subarachnoid hemorrhage, intermittent claudication, critical limb ischemia, asthma and organ failure after general surgery or transplantation (page 7, line 55 to page 8, line 5), thus fulfilling the specific embodiment of claims 1 and 9, specifying and endothelin antagonist and claim 2 specifying a vascular disease. Bradbury discloses the administration of the endothelin antagonists with another pharmaceutical agent known in the art to be of value in the treatment of the above diseases (page 9, lines 52-55), such as an ACE inhibitor (page 9, lines 55 to page 10, line 3), in combination therapy, thus fulfilling the specific embodiment of claim 20. The disclosure of Bradbury meets the specific embodiments of claims 1 and 9 because claims 1 and 9 encompass the endothelin antagonists in association with the active agent, and a mixture of the antagonist with the active agent fulfills the specific embodiments of the claims.
Bradbury also discloses a composition in suitable form for oral administration (page 9, lines 48-51), thus fulfilling the specific embodiment of claim 24.

14. Claims 1, 2, 9, 17 and 24 are rejected under 35 U.S.C. 102(e) as being anticipated by Hunt (EP 640,596 A1).

The specific embodiments of claims 1, 2, 9 and 24 are set forth above. Claim 17 embodies the method of claim 9 wherein the active agent is derived from heparin, hirudin, low molecular weight heparin or marcumar.

Hunt discloses a method of treating endothelin-mediated disorders comprising administration of antagonists of ET-1, ET-2 or ET-3 (page 5, line 23 to page 6, line 7) which include vascular diseases (page 5, line 44). Hunt discloses that the antagonists of the invention can be administered with thrombin inhibitors such as hirudin, modulators of PDGF activity, PAF antagonists, ACE inhibitors, calcium channel blockers, beta-andrenergeric agents, diuretic,

thrombolytic agents, and immunosuppressive agents (page 6, lines 8-24), thus fulfilling the specific embodiments of claims 1 and 9 because claims 1 and 9 encompass the endothelin antagonists in association with the active agent, and a mixture of the antagonist with the active agent fulfills the specific embodiments of the claims. The disclosure of the endothelin receptor antagonists in combination with hirudin meets the specific embodiment of claim 17. Hunt discloses formulations for oral administration (page 6, lines26-30) which fulfills the specific embodiment of claim 24.

15. Claims 9 and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Database Caplus, Accession Number 314384, (1995).

The abstract of Accession Number 314384 discloses an anti-endothelin antibody and radiolabled endothelin, which meets the specific embodiments of claim 9 drawn to endothelin and the antibody as the active group. The abstract anticipated claim 10 as well because endothelin is the first compound listed in claim 10.

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a)

18. Claims 1-3, 9, 10 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over the abstract of Bagnato et al (Proc Ann Meet Am Assoc Cancer Research, 1995, Vol. 36, page A287) and the abstract of Ishikawa et al (Journal of Cardiovascular Pharmacology, 1992, Vol. 20, suppl.12, pp. S11-S14) in view of Schwartz et al (US 4,504,476).

Claim 21 embodies the compound of claim 9 wherein the active group is derived from verapamil, nifedipine or diltiazem.

The abstract of Bagnato et al teaches that ET-1 is produced by ovarian cancer cells and acts as an autocrine growth factor on ETA receptors to stimulate calcium signaling resulting in proliferation. The abstract suggests that ET-1 participates in the progression of neoplastic growth in certain ovarian tumors.

The abstract of Ishikawa et al teaches BQ-123 which is cyclo(D-Trp-D-Asp-Pro-D-Val-Leu) as a selective ETA receptor antagonist.

Schwartz et al teach that verapamil, nifedipine and diltiazem are commercially available calcium channel blockers.

It would have been prima facie obvious at the time the claimed invention was made to administer cyclo(D-Trp-D-Asp-Pro-D-Val-Leu) together with verapamil, nifedipine or diltiazem for the treatment of ovarian tumors expressing ET-1. One of skill in eh art would have been motivate to do so by the teachings of the abstract of Bagnato et al on the participation of ET-1 in the progression of neoplastic growth by means of the autocrine/paracrine action of ET-1 on the ovarian tumors. One of skill in the art would be motivated to provide an antagonist to ET-1 in order to decrease the ability of ET-1 to stimulate ETA receptor and thereby activate calcium signaling which results in proliferation. One of skill in the art would be motivated to additionally provide a calcium channel blocker in order to decrease calcium channel signaling taught by the abstract of Bagnato et al to be a mediator of tumor cell proliferation.

19. Claims 1-3, 9, 10 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kitano et al (US 5,514,711) in view of the abstract of Bagnato et al (Proc Ann Meet Am Assoc Cancer Research, 1995, Vol. 36, page A287).

Claim 13 embodies the compound of claim 9 wherein the active group is derived from a quercetin, genistein, lavendustin A, herbimycin A, aeroplysinin-1-tyrphostin-S-aryl-benylidene malononitrile or benzylidene malononitril radical.

Kitano et al teach the tyrosine kinase inhibitors of genistein, erbstatin, lavendustin and benzylidenemalonitrile derivatives. Kitano et al teach that tyrosine kinase type receptors participate substantially in formation of cancer and that protein tyrosine kinase activity is high in cancer cells (COLUMN LINE). Kitano et al teach that the tyrosine kinase inhibitors of genistein, erbstatin, lavendustin and benzylidenemalonitrile derivatives can inhibit specifically the tyrosine kinase activity (column 1, lines 17-32) but that these compounds alone are not effective alone for the treatment of cancer (column 1, lines 43-45). Kitano et al do not teach genistein, erbstatin, lavendustin and benzylidenemalonitrile derivatives in association with antagonists of endothelin for the treatment of cancer.

The abstract of Bagnato et al teaches that ET-1 is produced by ovarian cancer cells and acts as an autocrine growth factor on ETA receptors and stimulating proliferation of said cells. The abstract suggests that ET-1 participates in the progression of neoplastic growth in certain ovarian tumors.

The abstract of Ishikawa et al (Journal of Cardiovascular Pharmacology, 1992, Vol. 20, suppl.12, pp. S11-S14) teaches BQ-123 which is cyclo(D-Trp-D-Asp-Pro-D-Val-Leu) as a selective ETA receptor antagonist..

It would have been prima facie obvious at the time the claimed invention was made to administer cyclo(D-Trp-D-Asp-Pro-D-Val-Leu) together with genistein, erbstatin, lavendustin or benzylidenemalonitrile derivatives for the treatment of tumors expressing ET-1. One of skill in eh art would have been motivate to do so by the teachings of the abstract of the abstract of Bagnato et al which identifies ET-1 as a paracrine/autocrine factor produced by the ovarian cancer cells and resulting in proliferation of said cells. One of skill in the art would recognize that the administration of a ET-1 antagonist would reduce the paracrine/autocrine stimulation by the ET-1 and decrease the proliferative response to ET-1, by interrupting the "loop" of autocrine/paracrine stimulation. One of skill in the art would have been motivated to do so to provide an antagonist to ET-1 in order to decrease the ability of ET-1 to stimulate ETA receptor

in combination with known anti-cancer compounds such as the tyrosine kinase inhibitors taught y Kitano et al in order to maximize the therapeutic efficacy of the treatment.

20. Claims 1, 2, 9 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Spellmeyer et al (WO 94/03483) in view of LaRochelle et al (US 5,468,468) and Battistini et al (Peptides, 1993 Mar-Apr, Vol. 14, pp.385-399).

Spellmeyer et al (WO 94/03483) teach antagonists of endothelin 1 (ET-1) that inhibit the binding of ET-1 to the endothelin receptor (page 19, lines 8-10, page 24, lines 19-20). Spellmeyer et al suggest that the inhibitors can be used to treat conditions modulated by endothelin which include pulmonary carcinoma (page 8, lines 8-9). Spellmeyer et al does not teach the administration of the antagonists in combination with anti-PDGF antibodies.

The abstract of Battistini et al teaches that ET-1 acts synergistically with EGF, PDGF, bFGF, TGF, insulin, etc to promote cellular transformation or proliferation and that the aforesaid factors may act to stimulate the synthesis and release of endothelins. The abstract teaches that the production and release of endothelins in acute and chronic pathological processes such as atherosclerosis, post-angioplastic restinosis, hypertension and carcinogenesis and that the endothelins are postulated to act in a paracrine/autocrine manner in growth regulation and play and important role in mediating vascular remodeling and in some cardiac diseases.

LaRochelle et al (US 5,468,468) teach antagonistic antibodies to PDGFR (column 2, lines 56-62). LaRochelle et al teach that said antibodies are potent antagonist capable of controlling or interfering with PDGF dependent autocrine growth associated with neoplasias, arteriosclerosis, fibrotic diseases and other pathological diseases known to be associated with PDGFR expression (column 2, lines 41-47).

It would have been prima facie obvious at the time the claimed invention was made to administer the antagonists of ET-1 as taught by Spellmeyer et al in combination with an anti-PDGF antibody for the treatment of cancer. One of skill in the art would have been motivated to do so by the teachings of Battistini et al on the synergistic interaction between ET-1 and PDGF in the promotion of cellular proliferation. One of skill in the art would be motivated to inhibit cellular proliferation by decreasing the PDGF available for stimulating the further synthesis and release of ET-1. One of skill in the art would be motivated to administer the antagonists of

Spellmeyer to prevent the binding of ET-1 to its receptor in order to interrupt the paracrine/aurocrine loop which promotes cell proliferation.

21. Claims 1, 2, 9, 12, 19, 20 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sohda et al (EP 562,599 A1).

The specific embodiments of the claims are set forth above.

Sohda et al teach a method for treating inflammatory joint diseases such as choric rheumatoid arthritis comprising administering endothelin receptor antagonists (page 12, lines 29-33). Sohda et al teach compositions for oral administration (page 12, lines 34-36) fulfill the specific embodiments of claim 24. Sohda et al teach that the compounds of the invention as superior in the treatment of rheumatoid arthritis than the administration of cortisone, adrenalcortical hormones, non-steroidal anti-inflammatory agents, anti-rheumatic agents, gold agents, anti-gout agents such as colchicine and immunosuppressants such as cyclophosphamide, azathioprine, methotrexate and levamisole (page 2, lines 19-29). Sohda et al do not teach the treatment of inflammatory bone disease with a combination of the endothelin receptor antagonists and cochicine, cyclophosphamide, or methotrexate.

It would have been prima facie obvious at the time the claimed invention was made to co-administer the endothelin receptor antagonists and a therapeutic agent such as cochicine, cyclophosphamide, or methorexate. One of skill in the art would have been motivated to do so because both the endothelin receptor antagonists and the cochicine, cyclophosphamide, and methorexate were recognized as providing some use in treating the same disorder.

22. Claims 1, 2, 9, 15 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cody et al (US 5,382,569) in view of Arita et al (US 5,478,838).

Cody et al teach antagonists of endothelin useful in treating elevated levels of endothelin, acute and chronic renal failure, hypertension, myocardial infarction, metabolic, endocrinological, neurological disorders, congestive heart failure, endotoxic shock, subarachnoid hemorrhage, arrhythmias, asthma, pre-eclampsia, Raynaud's disease, percutaneous transluminal coronary angioplasty or restenosis, angina, cancer, pulmonary hypertension, ischemic disease, gastric mucosal damage, ischemic bowel disease, and diabetes (column 1, lines 10-26). Cody et al teach

that the compositions can also comprise other compatible therapeutic agents (column 47, lines 19-20). Cody et al do not specifically teach the administration of the antagonists of endothlein and trizolopyrimidine. Cody et al teach that the compounds of the invention include compositions suitable for oral administration (column 45, line 67 to column 46, line 21), thus fulfilling the specific embodiment of claim 24.

Arita et al teach triazolopyrimidine (column 8, line 2) for the treatment of hypertension (column 5, lines 33-36).

It would have been prima facie obvious at the time the claimed invention was made to administer a combination of the endothelin antagonists of Cody et al and trizolopyrimidine for the treatment of hypertension. One of skill in the art would have been motivated to do so because both compounds are taught by the prior art to be useful in the treatment of hypertension.

23. Claims 1, 2, 9, 15, 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hunt (EP 640,596 A1) in view of LaRochelle et al (US 5,468,468).

The specific embodiments of claims 1, 2, 9 and 24 are set forth above. Claim 17 embodies the method of claim 9 wherein the active agent is derived from heparin, hirudin, low molecular weight heparin or marcumar.

Hunt teaches a method of treating endothelin-mediated disorders comprising administration of antagonists of ET-1, ET-2 or ET-3 (page 5, line 23 to page 6, line 7) which include vascular diseases (page 5, line 44). Hunt teaches that the antagonists of the invention can be administered with thrombin inhibitors such as hirudin, modulators of PDGF activity, PAF antagonists, ACE inhibitors, calcium channel blockers, beta-andrenergeric agents, diuretic, thrombolytic agents, and immunosuppressive agents (page 6, lines 8-24), thus fulfilling the specific embodiments of claims 1 and 9 because claims 1 and 9 encompass the endothelin antagonists in association with the active agent, and a mixture of the antagonist with the active agent fulfills the specific embodiments of the claims. The disclosure of the endothelin receptor antagonists in combination with hirudin meets the specific embodiment of claim 17.

LaRochelle et al (US 5,468,468) teach antagonistic antibodies to PDGFR (column 2, lines 56-62). LaRochelle et al teach that said antibodies are potent antagonist capable of controlling or interfering with PDGF dependent autocrine growth associated with neoplasias,

arteriosclerosis, fibrotic diseases and other pathological diseases known to be associated with PDGFR expression (column 2, lines 41-47).

It would have been prima facie obvious at the time the invention was made to use the anti-PDGF antibody taught by LaRochelle et al in the method of treating endothelin mediated disorders as taught by Hunt et al. One of skill in the art would have been motivated to do so by the suggestion of Hunt et al that modulators of PDGF activity are part of the claimed invention.

24. Claims 1, 2, 9, 20, 22 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bradbury (EP 682,016 A1) in view of the abstract of Olsson et al (Drugs, 1988, Vol. 36 Suppl 3, pp. 115-120).

The specific embodiments of claims 1, 2, 9 and 24 are set froth above. Claim 20 embodies the method of claim 9 wherein the active group is derived from cochicine, angiopeptin, estrodiol or an ACE inhibitor.

Bradbury discloses a method of treating diseases in which abnormal levels of endothelin play a causative role comprising the administration of endothelin antagonists of formula I, wherein examples of said diseases are hypertension, pulmonary hypertension, congestive heart failure, dyslipidaemia, artherosclerosis, restinosis, acute and chronic renal failure, stroke, subarachnoid hemorrhage, intermittent claudication, critical limb ischemia, asthma and organ failure after general surgery or transplantation (page 7, line 55 to page 8, line 5), thus fulfilling the specific embodiment of claims 1 and 9, specifying and endothelin antagonist and claim 2 specifying a vascular disease. Bradbury discloses the administration of the endothelin antagonists with another pharmaceutical agent known in the art to be of value in the treatment of the above diseases (page 9, lines 52-55), such as an ACE inhibitor (page 9, lines 55 to page 10, line 3), in combination therapy, thus fulfilling the specific embodiment of claim 20. The disclosure of Bradbury meets the specific embodiments of claims 1 and 9 because claims 1 and 9 encompass the endothelin antagonists in association with the active agent, and a mixture of the antagonist with the active agent fulfills the specific embodiments of the claims.
Bradbury also discloses a composition in suitable form for oral administration (page 9, lines 48-51), thus fulfilling the specific embodiment of claim 24.

The abstract of Olsson et al teaches a method of treating hyperlipidemia, which is synonymous with dyslipidaemia, comprising the administration of simvastatin or probucol.

It would have been prima facie obvious at the time the invention was made to administer a combination of endothelin inhibitors and simvastatin or probucol. One of skill in the art would have been motivated to do so because both the endothlein antagonists and simvastatin and probucol are taught by the prior art to be useful in the treatment of dyslipidaemia.

25. Claims 1, 2, 9, 17, 21 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hunt in view of the abstract of Saseen et al (Ann Pharmacother, 1996 Jul-Aug, Vol. 30, pp. 802-810).

Claim 21 embodies the method of claim 9 wherein the active group is derived from verapamil, nifedipine or diltiazem.

Hunt teaches a method of treating endothelin-mediated disorders comprising administration of antagonists of ET-1, ET-2 or ET-3 (page 5, line 23 to page 6, line 7) which include vascular diseases (page 5, line 44). Hunt teaches that the antagonists of the invention can be administered with thrombin inhibitors such as hirudin, modulators of PDGF activity, PAF antagonists, ACE inhibitors, calcium channel blockers, beta-andrenergeric agents, diuretic, thrombolytic agents, and immunosuppressive agents (page 6, lines 8-24), thus fulfilling the specific embodiments of claims 1 and 9 because claims 1 and 9 encompass the endothelin antagonists in association with the active agent, and a mixture of the antagonist with the active agent fulfills the specific embodiments of the claims. The disclosure of the endothelin receptor antagonists in combination with hirudin meets the specific embodiment of claim 17. Hunt teaches formulations for oral administration (page 6, lines26-30) which fulfills the specific embodiment of claim 24. hunt et al doses not specifically teach the administration of the endothelin antagonists with verapamil, nifedipine or diltiazem.

The abstract of Saseen et al identifies verapamil, nifedipine and diltiazem as calcium channel blockers useful for the treatment of hypertension.

It would have been prima facie obvious at the time the claimed invention was made to administer the endothelin antagonists of Hunt in combination with verapamil, nifedipine or diltiazem. One of skill in the art would have been motivated to do so by the teachings of Hunt

that the endothelin antagonists can be administered with calcium channel blockers and the teachings of the abstract of Saseen et al identifying verapamil, nifedipine or diltiazem as clinically useful anti-hypertensive agents which are calcium channel blockers.

26. Claims 1, 2, 9, 17, 18 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hunt in view of Lauwereys et al (WO 94/20535).

Claim 18 embodies the compound of claim 9, wherein the active group is derived from factor VIIa or Xa inhibitors.

Hunt teaches a method of treating endothelin-mediated disorders comprising administration of antagonists of ET-1, ET-2 or ET-3 (page 5, line 23 to page 6, line 7) which include vascular diseases (page 5, line 44). Hunt teaches that the antagonists of the invention can be administered with thrombin inhibitors such as hirudin, modulators of PDGF activity, PAF antagonists, ACE inhibitors, calcium channel blockers, beta-andrenergeric agents, diuretic, thrombolytic agents, and immunosuppressive agents (page 6, lines 8-24), thus fulfilling the specific embodiments of claims 1 and 9 because claims 1 and 9 encompass the endothelin antagonists in association with the active agent, and a mixture of the antagonist with the active agent fulfills the specific embodiments of the claims. The disclosure of the endothelin receptor antagonists in combination with hirudin meets the specific embodiment of claim 17. Hunt teaches formulations for oral administration (page 6, lines26-30) which fulfills the specific embodiment of claim 24. Hunt et al doses not specifically teach the administration of the endothelin antagonists with a factor VIIa inhibitor or a factor Xa inhibitor.

Lauwereys et al teach the administration of Ecotin as an antithrombotic agent (page 19, lines 17-30). Lauwereys et al teach that Ecotin is an inhibitor of factor Xa, which meets the specific embodiment of claim 18.

It would have been prima facie obvious at the time the invention was made to administer the endothelin antagonists of Hunt in combination with Ecotin. One of skill in the art would have been motivated to do so by the teachings of Hunt that the endothelin antagonists can be administered with thrombin inhibitors, and the teachings of Lauwereys et al that Ecotin is an antithrombotic agent.

27. Claims 1, 2, 3, 9, 10, 16, 19, 21, 23 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Low et al (WO 96/36367) in view of Chan (WO 95/13374)

Low et al teach a method for introducing active agents into cells comprising administering a complex formed between an active agent an a ligand, wherein said binding of said ligand to the receptor induced receptor-mediated endocytosis (page 2, line 20 to page 3, line 23). Low et al teach the ligand of biotin, receptor-binding analogs of biotin, folate, receptor-binding analogs of folate, riboflavin, or receptor-binding analogs of riboflavin (abstract). Low et al teach that any manner of forming a complex between an exogenous molecule of interest and a ligand capable of triggering receptor mediated endocytosis can include covalent, ionic, or hydrogen bonding either directly, or indirectly through a linking group and that art-recognized biologically labile covalent linkages are preferred when the exogenous molecule is found to have reduced functionality in the complexed form (page 11, line 28 to page 12, line 9). Low et al also teach that the ligands can be conjugated to liposome-forming phospholipids and used to deliver exogenous molecules capable of modulating or otherwise modifying cell function (page 17, lines 10-16). Low et al teach the delivery of exogenous molecules including aspirin which meets the specific embodiment of claim 16 specifying an acetylsalicylic acid, beta-blockers, antihypertensive agents including verapamil and nifedipine, which meets the specific embodiments of the instant claim 21, cardiovascular agents, chemotherapeutic agents, anti-inflammatory substances, which meet the specific embodiments of claim 19, drawn to a anti-inflammatory agent, anti-emetics (page 9, line 31 to page 10, line 34) and anti-sense polynucleotides (page 11, lines 5-6 and page 16, lines 33-35), thus fulfilling the specific embodiment of claim 23 specifying an active group which is an anti-sense oligonucleotide. Low et al contemplate that other receptors used to deliver nutrients into cells and which undergo receptor mediated endocytosis can be used to deliver active substances into cells (page 17, line 33 to page 18, line 8). Low et al teach compositions for oral administration routes which fulfills the specific embodiment of claim 24. Low et al does not specifically contemplate ligands which bind to the endothelin receptor as a means of delivering said exogenous molecules into cells.

It is noted that the first structure in claims 3 and 10 is endothelin.

Chan teaches that the endothelin receptor undergoes receptor mediated endocytosis and can be used to deliver DNA into cells (page 14, lines 6-15).

It would have been prima facie obvious at the time the claimed invention was made to substitute endothelin for the ligand binding receptor in the method of Low et al. One of skill in the art would have been motivated to do so by the teachings of Chan which identify the endothelin receptor as capable of undergoing receptor induced endocytosis. One of skill in the art would have a reasonable expectation of success that by linking an exogenous molecule to endothelin, either via known linkers or via a liposome, said exogenous molecule would be internalized by cells when endothelin bound to the endothelin receptor.

Double Patenting

28. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

29. Claims 9-24 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 5-16 and 25-32 of U.S. Patent No. 6,291,639. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 9-24 are obvious variants of claims 5-16. Conjugates with "peptides, proteins, bio-molecules or macromolecules as their complexes with metal ions and hydrosoluble salts" encompasses the instant embodiment of W1 which stands for an active group that contains a

radionuclide At, Ba, Bra, C, F, N, O or P, or that is derived from a chemotherapy agent, an antibody, an antibody fragment, peptide, carbohydrate, oligoucleotide, PTK blocker, antithrombotic agent, growth factor inhibitor, pharmaceutical agent, hormone, platelet aggregation inhibitor, anti-inflammatory agent, Ca-antagonist, lipid-lowering agent or anti-proliferative agent. Further, claims 25, 27, 29 and 31 specify that the comprises endothelin and claims 26, 28, 30 and 32 are drawn to the same structures as the instant claim 10.

30. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10 a.m. to 9 p.m. M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571)272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.
10/18/2004

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